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DOI:

[10.1183/16000617.00009014](https://doi.org/10.1183/16000617.00009014)

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*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Turner, AM, Tamasi, L, Schleich, F, Hoxha, M, Horvath, I, Louis, R & Barnes, N 2015, 'Clinically relevant subgroups in COPD and asthma', *European Respiratory Review*, vol. 24, no. 136, pp. 283-98.  
<https://doi.org/10.1183/16000617.00009014>

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# Clinically relevant subgroups in COPD and asthma

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**ABSTRACT** As knowledge of airways disease has grown, it has become apparent that neither chronic obstructive pulmonary disease (COPD) nor asthma is a simple, easily defined disease. In the past, treatment options for both diseases were limited; thus, there was less need to define subgroups. As treatment options have grown, so has our need to predict who will respond to new drugs. To date, identifying subgroups has been largely reported by detailed clinical characterisation or differences in pathobiology. These subgroups are commonly called "phenotypes"; however, the problem of defining what constitutes a phenotype, whether this should include comorbid diseases and how to handle changes over time has led to the term being used loosely.

In this review, we describe subgroups of COPD and asthma patients whose clinical characteristics we believe have therapeutic or major prognostic implications specific to the lung, and whether these subgroups are constant over time. Finally, we will discuss whether the subgroups we describe are common to both asthma and COPD, and give some examples of how treatment might be tailored in patients where the subgroup is clear, but the label of asthma or COPD is not.



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**Summary of subgroups of airways disease that can be found in COPD and asthma, and their management** <http://ow.ly/KiDvo>

## Introduction

As knowledge of airways disease has grown, it has become apparent that neither chronic obstructive pulmonary disease (COPD) nor asthma is an easily defined disease. Various new definitions have been proposed [1–3], largely focusing on identifying subgroups by detailed clinical characterisation or differences in pathobiology. These subgroups are commonly called "phenotypes" and in some cases correspond with the Oxford English Dictionary definition of a phenotype: "The sum total of the observable characteristics of an individual, regarded as the consequence of the interaction of the individual's genotype with the environment". This definition does not include treatment or prognosis, but has strengths in that it helps us to observe clusters of characteristics and delineate new phenotypes where,

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Received: July 21 2014 | Accepted after revision: Sept 22 2014

**Support statement:** This study was not supported by any specific funding, although the authors met and began the process of researching the review at an educational event sponsored by GSK. L. Tamasi has received funding from the Hungarian Respiratory Society. F. Schleich and R. Louis have been supported by the Interuniversity Attraction Poles (IAP) Project, Brussels, Belgium (P6/35 and P7/30).

**Conflict of interest:** Disclosures can be found alongside the online version of this article at [err.ersjournals.com](http://err.ersjournals.com)

**Provenance:** Submitted article, peer reviewed.

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many years later, further research can lead to treatment. However, the utility of some phenotypes in clinical practice remains uncertain due to inconsistency of definition, accumulation of comorbid diseases, the propensity of both asthma and COPD to change over time, and the lack of a clear relationship with defined treatment strategies.

In this review we describe a series of clinically relevant subgroups in COPD and asthma, *i.e.* patients with clearly defined clinical characteristics (phenotype) and whom we believe have prognostic or therapeutic implications specific to the lung. Using this definition, commonly associated comorbidities would not be part of the way the subgroup was defined unless the cluster of comorbidities were specific to COPD or asthma, or altered pulmonary management. Behavioural characteristics, such as poor compliance with treatment, would also fall outside our subgroups as they affect many diseases equally. We will also review the evidence for the stability of these subgroups over time, the degree to which they overlap between COPD and asthma, and what this implies for therapy.

### Clinically relevant subgroups in COPD

COPD is an umbrella term covering many underlying processes that may lead to fixed airflow obstruction. Several large clinical trials and cohort studies have begun to delineate COPD subgroups where there is a clear treatment implication (table 1). A number of other subgroups, where the picture regarding treatment is not as clear or which are more clinically relevant because of their implication for prognosis than treatment, are shown in figure 1.

Comorbidity in COPD influences prognosis [29] and health-related quality of life (HRQoL) [30] and shares aspects of pathogenesis [31]. However, there remains considerable debate as to whether comorbid disease represents a specific subgroup. Common comorbidities in COPD include osteoporosis, ischaemic heart disease, anxiety and depression. Most common comorbidities impair outcome in COPD patients, have clear treatment implications if present, and are treated similarly whether the patient has COPD or not (table 2). These treatments are not specific to the underlying airway disease and, thus, do not form part of our definition of a clinically relevant subgroup.

TABLE 1 Subgroups of chronic obstructive pulmonary disease (COPD) that currently have specific treatments

Subgroup	Treatment	Effect of treatment	[Ref.]
<b>Frequent exacerbator</b>	LABA, LAMA, LABA/ICS, roflumilast, macrolides	Reduced exacerbations, better HRQoL, improved lung function, possible effect on FEV <sub>1</sub> decline <sup>¶</sup> and mortality <sup>¶</sup>	[4–11]
<b>Chronic bronchitis</b>	Roflumilast, mucolytics	Reduced exacerbations, improved HRQoL	[12–14]
<b><math>\alpha_1</math>-antitrypsin deficiency</b>	$\alpha_1$ -antitrypsin augmentation	Reduced progression of emphysema	[15]
<b>Upper zone dominant emphysema and bullous emphysema</b>	LVRs	Improved lung function, reduced exacerbations	[16, 17]
<b>Type 1 respiratory failure</b>	LTOT	Improved survival and HRQoL	[18, 19]
<b>Type 2 respiratory failure</b>	Domiciliary NIV	Improved survival, possible effect on hospital admissions and HRQoL	[20–24]
<b>Eosinophilic COPD<sup>#</sup></b>	Steroids	Reduced exacerbations, improved lung function	[25–27]
<b>Biomass COPD</b>	Removal of biomass exposure	Reduced FEV <sub>1</sub> decline	[28]

Frequent exacerbator, chronic bronchitis and  $\alpha_1$ -antitrypsin deficiency are stable over time; the other subgroups may vary according to disease severity or evidence is not yet clear. LABA: long-acting  $\beta$ -agonists; LAMA long-acting muscarinic antagonists; ICS: inhaled corticosteroids; HRQoL: health-related quality of life; FEV<sub>1</sub>: forced expiratory volume in 1 s; LVRs: lung volume reduction surgery; LTOT: long-term oxygen therapy; NIV: noninvasive ventilation. <sup>#</sup>: see "Subgroups shared between COPD and asthma" section; <sup>¶</sup>: effect only reported for LABA/ICS.

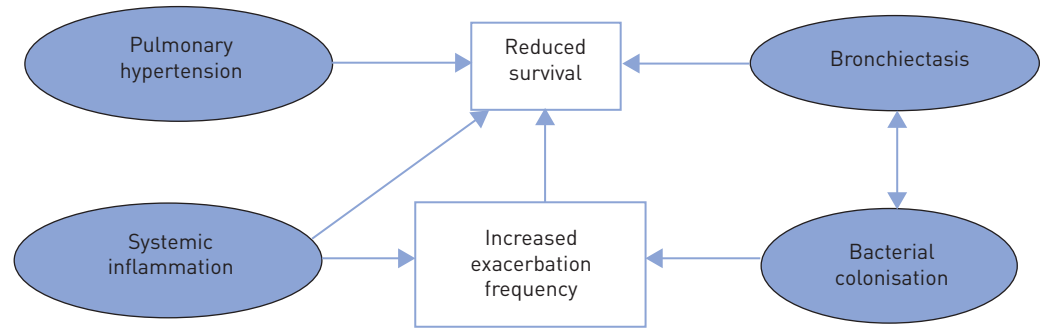


FIGURE 1 Chronic obstructive pulmonary disease subgroups without clear treatment implications. The figure shows the subgroups with clear prognostic implications for patients that are clinically relevant, but where therapeutic strategies are as yet unclear. The directions of the arrows indicate the probable direction of the association, e.g. patients with more frequent exacerbations are less likely to survive. The direction of association of bacterial colonisation and bronchiectasis is not clear; thus, a bidirectional arrow is shown.

The only possible exception to this is osteoporosis, which is almost twice as common in subjects with airflow obstruction compared to those without [48], is particularly associated with emphysema [40] and has been shown to change with pulmonary treatment (e.g. lung volume reduction surgery (LVRS)). A prospective cohort study [49] looking at the effect of LVRS on bone mineral density (BMD) in patients with severe COPD concluded that surgery significantly improved BMD compared to pulmonary rehabilitation. The increase correlated with residual volume, diffusing capacity of the lung for carbon monoxide and fat-free mass, suggesting that restoration of respiratory dynamics, gas exchange and nutritional status induced an improvement in bone metabolism and mineral content independent of exercise. However, changes in BMD could occur with increased activity resulting in the beneficial effect of LVRS and may have confounded results. Furthermore, most interventional studies of osteoporosis outside COPD show more modest BMD improvement, generally in the range of 3–8% [41], whereas LVRS patients in this study improved by up 24%, suggesting that the result should be interpreted with caution. The degree to which the relationship between osteoporosis and emphysema is confounded by prior steroid treatment is not clear, but there are male patients with little or no steroid exposure who develop osteoporosis, suggesting that it may not be entirely iatrogenic [50]. However, further studies are indicated to understand mechanisms and determine optimal treatment.

TABLE 2 Common comorbidities in chronic obstructive pulmonary disease (COPD)

Comorbidity	Effect/associations of comorbidity in COPD	Treatment	[Ref.]
<b>Ischaemic heart disease</b>	Increased mortality	$\beta$ -blocker, ACE-I, aspirin, statin, nitrates	[32, 33]
<b>Congestive cardiac failure</b>	Increased symptom burden, increased mortality	As above, plus diuretics Digoxin and implantable devices may be used in some patients	[32, 34]
<b>Anxiety</b>	Poor HRQoL, increased mortality, increased hospital admissions	CBT, benzodiazepines, exercise	[35–37]
<b>Depression</b>	Poor HRQoL, increased mortality, increased hospital admissions	CBT, anti-depressants, exercise	[37–39]
<b>Osteoporosis</b>	Reduced physical performance, poor lung function	Calcium supplements, bisphosphonates	[40–44]
<b>GORD</b>	More frequent exacerbations	PPI, H2 receptor antagonist	[45–47]

This is not an exhaustive list of all conditions or treatments; where possible, references specific to COPD, major review articles or international guidelines on management have been cited rather than single studies. GORD: gastro-oesophageal reflux disease; ACE-I: angiotensin-converting enzyme inhibitor; HRQoL: health-related quality of life; CBT: cognitive behavioural therapy, PPI: proton-pump inhibitor.

### Subgroups with implications for treatment

Frequent exacerbators, defined as those with more than two exacerbations a year, were definitively described in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study [51]. Treatment options in this group include bronchodilators, long-acting  $\beta$ -agonists (LABA)/inhaled corticosteroids (ICS), roflumilast and azithromycin. In a number of trials, bronchodilation has been shown to reduce exacerbation frequency. Long-acting muscarinic antagonists (LAMA) appear to exhibit this as a class effect, e.g. tiotropium and glycopyrronium both reduced exacerbation frequency by >20% in the GLOW2 trial and were not statistically different in this regard [5]. A meta-analysis of LABAs showed a reduction in exacerbations that was close to 20%, although differences between them were reported; formoterol only reduced exacerbations when used alongside ICS, whereas salmeterol had an effect when used alone [6]. LAMA may be superior to LABA at reducing exacerbations, as shown in the POET (Prevention of Exacerbations of COPD) study (tiotropium *versus* salmeterol) [11]. LAMA/LABA also reduce exacerbation frequency, although the effect does not appear additive. For example, in the SPARK study (indacaterol and glycopyrronium), the combination only reduced exacerbations by a further 12% over monotherapy [52]. LABA/ICS have been demonstrated to improve lung function and HRQoL and to reduce exacerbations by ~25% in COPD patients [7]. Whilst most COPD trials have not focused on frequent exacerbators, international guidelines recognise the impact of certain drug classes on exacerbation frequency, emphasising the role of LABA/ICS [53]. Macrolides have become a hot topic throughout respiratory medicine, primarily because of their potential anti-inflammatory effects. In COPD, the largest study to date used azithromycin and prolonged time to first exacerbation from 174 to 266 days, implying it might be useful in frequent exacerbators [10]. Long-term safety issues include resistance and have been discussed elsewhere [54].

Chronic bronchitis occurs in 45% of COPD patients [55] and is linked to higher exacerbation frequency and, hence, risk of decline [56]. Specific therapies for patients with chronic bronchitis have been reviewed elsewhere [57]. Roflumilast appears to prevent exacerbations best in COPD patients who have chronic bronchitis [14], although utility may not be restricted to this group. Its use provided modest but significantly improved forced expiratory volume in 1 s (FEV<sub>1</sub>) compared with placebo and a reduction in exacerbations. Mucolytics have also been used to reduce sputum viscosity and aid expectoration; those most widely used are carbocysteine and *N*-acetylcysteine. Whilst trials have not been specific to chronic bronchitis, their mechanism of action suggests they will work best in chronic sputum producers. The most recent systematic review of clinical effectiveness of mucolytics included 30 studies and demonstrated a small, but statistically significant, reduction in exacerbations in treated COPD patients [12].

$\alpha_1$ -antitrypsin deficiency (AATD) is the textbook case of a subgroup in COPD. It is associated with lower zone dominant emphysema [58], although significant heterogeneity exists, possibly due to genetic modifiers, as in usual COPD [59]. Augmentation therapy for AATD has been routinely used in some countries since the first trials were completed; a meta-analysis has demonstrated that it may reduce emphysema progression [15]. Further trials, including inhaled  $\alpha_1$ -antitrypsin, are due to be published soon and other specific therapies may become available in due course [60].

Upper zone dominant emphysema, as defined by visual appearance on chest computed tomography scans, was specifically reported in the NETT (National Emphysema Treatment Trial) study, which demonstrated that LVRS works best in this group of patients [16]. Further research using endobronchial valves as a less invasive means of LVRS initially targeted this group [17]. *Post hoc* analyses suggest that whether fissures are intact may be more important than disease location or heterogeneity [61]. Patients with upper zone dominant emphysema also exhibit different genetic risk factors, implying variation in pathogenesis [62]. Bullous emphysema is also treated surgically, although patient selection and operative technique is much more individualised [63].

Overt or relative hypoxia occurs in COPD, especially in later stages. The basis for long-term oxygen therapy (LTOT; oxygen for >15 h per day) is derived from two landmark placebo-controlled randomised controlled trials, the NOTT (Nocturnal Oxygen Therapy Trial) study [18] and the MRC (Medical Research Council) study [19], which demonstrated improved survival. The NOTT study also demonstrated a decrease in mean pulmonary artery pressure. LTOT is indicated for stable patients who have an arterial oxygen tension <7.3 kPa on two separate occasions or 7.3–8.0 kPa in the presence of pulmonary hypertension, nocturnal hypoxia or secondary polycythaemia. LTOT is not restricted to type 1 respiratory failure; however, if used in type 2 patients, adverse effects on hypercapnia are generally excluded prior to prescription. Aside from LTOT, two other modes of oxygen therapy exist, ambulatory and short burst; both have been reviewed elsewhere [64]. Ambulatory oxygen is indicated in mobile patients who meet LTOT criteria and is commonly considered in others who exhibit exertional desaturation to <90%. Short-burst oxygen therapy criteria are poorly defined and no benefits have been reported [65].

Noninvasive ventilation (NIV) is used to treat type 2 respiratory failure and has a strong acute evidence base in hospital [66] for COPD patients. The evidence concerning use of home NIV in COPD is

contradictory and concerns have been raised about whether potential benefits on incidence of severe exacerbations and hospital admissions are appropriately balanced with poor HRQoL [20–23]. More recently, it has been shown to improve survival by 21% [24]; a systematic review is ongoing [67].

Eosinophilic COPD is a controversial area, mainly because of the issue of whether it is truly distinct from asthma (overlap pathologies will be discussed later). Recent evidence suggests it may be identified by sputum cytokine profile [68]. Nevertheless, trials focussing on such patients have been published and suggest that steroids are more beneficial in this group than in other COPD patients [25]. Several studies have reported that use of sputum eosinophilia as a guide to the use of steroids was effective [26, 27, 69], and systemic eosinophil counts may also be a useful guide to treating exacerbations with oral corticosteroids [70]. Recent evidence suggests that blood eosinophil counts  $>2\%$  predicted a response to ICS in several major COPD trials [71], although these were *post hoc* analyses and further definitive work in this area is awaited.

Biomass fuel COPD is common in females, particularly in the developing world [72]. Airway predominant phenotypes appear to be more common, with bronchial hyperresponsiveness (BHR) being a particular feature in wood smoke exposure [73]. Consistent with this is the reported increased prevalence of an overlap between asthma and COPD [74]. Systemic and pulmonary inflammation is similar to cigarette smoke-induced disease [75, 76], with less emphysema [77] and less rapid FEV<sub>1</sub> decline [78]. Patients decline more slowly if the biomass exposure is reduced [28], but is not clear whether inhaled therapies used for “usual COPD” are of similar efficacy. The presence of BHR and overlap with asthma suggests that ICS might be an effective strategy, though no clinical trials have been reported yet.

#### *Subgroups with less clear implications for therapy*

Pulmonary hypertension in COPD adversely affects survival and exercise capacity. Although oxygen therapy protects against progression of pulmonary hypertension in patients with advanced COPD, its use is limited to those meeting LTOT criteria. Vasoactive compounds used in primary pulmonary hypertension (sildenafil, bosentan and nitric oxide) have been investigated in COPD [79–83]. Some trials showed worsening HRQoL in treated patients, hence they are not used routinely, although individual patient trials are employed in selected patients by specialist centres [84].

Systemic inflammation appeared to mark a subgroup of patients in the ECLIPSE study. This subgroup comprised 16% of the whole group and had increased mortality and exacerbation rates compared to patients without inflammation [85]. It remains unclear whether this group should be treated differently; future trials of therapies aimed at reducing exacerbations might target this group, or include them as a pre-specified subgroup analysis.

Stable state airway bacterial colonisation occurs in 30–70% of COPD patients, and may relate to sputum colour [86–88]. It is defined as a significant pathogenic bacterial load (usually  $>1 \times 10^6$  cfu·mL<sup>-1</sup>) present in sputum when the patient is well. Airway bacterial colonisation is associated with increased pulmonary inflammation [89] and increased frequency of exacerbations [90]; hence, it seems a logical subtype to target. Differences between laboratories, local bacterial patterns and lack of consistency of culture results over time may impact significantly on our ability to use this as a phenotype that directs therapy. Moxifloxacin has been tested to limited clinical benefit (exacerbation rates did not fall, although changes in bacteriology were seen) [91], and a macrolide trial is ongoing [92].

There is growing recognition that bronchiectasis may occur in patients who have had COPD for some time, but its prevalence varies widely (30–70% of subjects), depending on the presence of AATD and the method used to define bronchiectasis on computed tomography [93, 94]. Again it is unclear whether treatment should differ, even though there are implications for survival (COPD with bronchiectasis *versus* COPD without bronchiectasis, hazard ratio 2.54) [95] and recovery time from exacerbations [96]. Exacerbation frequency has not been found to differ [95, 96], although colonisation is more common [96].

Airflow obstruction, aetiology of which is thought to be due to tuberculosis [97], is a poorly defined phenotype as it is not clear whether the underlying prognosis is the same as classical smoking-related COPD or whether treatment should differ. It is likely that pathogenesis differs, but this has not been investigated fully. Many clinicians will adopt treatment approaches outside the guidelines for “usual COPD”, but it remains important to emphasise to non-specialists that not all fixed airflow obstruction is “usual COPD”. Early life events that impact on lung function [98] seem unlikely to be amenable to therapy later in life, but this too remains uncertain.

#### *Constancy of COPD subgroups*

In general, COPD is regarded as a disease that is slowly progressive; thus, it should be relatively easy to select a treatment at a given time-point that will remain useful for some time. However, there has been little research into the progression of the subgroups we have proposed. It may be much harder to propose



a specific therapy for those that vary unless very detailed monitoring is undertaken or the duration of therapy is fixed.

There are a number of COPD subgroups that remain constant once present. The frequent exacerbator subgroup was relatively stable in the ECLIPSE study [51], as was systemic inflammation [85]. Whilst therapies that target exacerbations may reduce their frequency [4], this positive treatment effect does not detract from the fact that patients on a range of treatments in the ECLIPSE study still exhibited stable exacerbation frequency, enabling it to be considered a sufficiently stable feature to guide treatment. Chronic bronchitis is defined as sputum production on most days for at least 3 months within at least 2 consecutive years [99], and consequently is probably constant enough to guide therapy. By definition, AATD is a constant phenotype as it is determined by genotype.

Other subgroups appear to develop over time but are sufficiently constant to guide therapy decisions over a few years. Upper zone dominant emphysema has not been studied longitudinally in usual COPD; however, in AATD, it is an early event prior to the development of lower zone dominant emphysema followed by homogenous disease [100]. This occurs over many years; thus, it is probably constant enough to guide decision making on treatment such as chronic bronchitis. Longitudinal blood gas studies have not been commonly carried out in COPD, although type 2 failure does develop over time, occurring in 24% of patients who have had an acidotic hypercapnic exacerbation 5 years after the first event [101]. Predictors of hypoxia and hypercapnia include lung function and body composition [102]. What data are available suggest that progression of blood gas changes occurs in COPD, but that changes are slow enough (outside exacerbations) to enable gases to be used to guide therapy.

Phenotypes where variation occurs over time are also seen in COPD. Pulmonary hypertension usually occurs late in disease [103], although it can occur alongside mild COPD [104]. Probably the only relevant clinical feature to define constancy is whether it is ever reported to disappear once it has developed; intuitively one would imagine that it is as constant as the degree of respiratory failure though this is not supported by published evidence. One small study has shown that pulmonary artery pressure varies with exacerbations and exercise [105]; animal studies also imply phases of remission [106]. There have been few published studies detailing longitudinal changes in sputum bacterial content in stable COPD. Data in AATD suggests that it does not always stay the same [107], *Moraxella catarrhalis* and *Pseudomonas aeruginosa* are capable of spontaneous remission in COPD [108, 109], and serial cultures during clinical trials also demonstrate variability [10]. It seems unlikely that colonisation can be defined on the basis of a single sputum culture when stable, but it might become a sufficiently constant phenotype to guide therapy if the definition can be better clarified.

### Clinically relevant subgroups in asthma

Bronchial asthma is a complex disease with many underlying mechanisms and, therefore, can be considered a syndrome containing subgroups with important similarities but also differences caused by variable underlying aetiologies [1]. Some subgroups described in the literature are based on clinical features found in asthma databases and cluster analyses; molecular and genetic approaches have also been widely used [110]. This merging of clinical and pathological features has been reviewed extensively elsewhere [111], using the term endotype to delineate this way of defining disease. Within this review, we have chosen to focus on clinically relevant subgroups rather than endotypes, as this may be more useful in clinical practice, although discussion of some molecular elements is unavoidable.

#### Subgroups with treatment implications

A number of distinct asthma phenotypes have treatment implications and are summarised in table 3. There is a degree of overlap in that aspirin-sensitive asthma (ASA), which is caused by increased cysteinyl leukotriene production exacerbated by nonsteroidal anti-inflammatory drugs, is often accompanied by severe eosinophilic rhinosinusitis and nasal polyps. Therefore, it has many features of atopic/allergic asthma, which is often eosinophilic, and is associated with elevated IgE, exhaled nitric oxide fraction (FeNO) and periostin levels [125]. Nonatopic, noneosinophilic asthma typically demonstrates lower airway hyperresponsiveness [126, 127] and lower corticosteroid responsiveness [127].

Based on cluster analysis [128], age at disease onset is a key differentiating factor linked to underlying genetic/molecular features, although it does not influence treatment directly. Nevertheless, it is clear that certain asthma subgroups, which vary with age, will require different treatment. Early-onset asthma is often more atopic/allergic, and *ORMDL3* polymorphisms exhibit a stronger association with childhood and severe asthma [129, 130]. These observations suggest that there are different disease mechanisms in younger patients, which have been partly proven by studies of airway cells. Four inflammatory subgroups are distinguishable in induced sputum: eosinophilic, neutrophilic, paucigranulocytic and mixed granulocytic [131]. For the purposes of treatment, this tends to be divided into eosinophilic and noneosinophilic disease. Supporting this simplified sub-division, molecular phenotyping showed a

TABLE 3 Asthma subgroups and their stability over time

Subgroup	Treatment	[Ref.]
<b>Atopic/allergic</b>	Avoidance of triggers, ICS, CS, anti-IgE, anti-IL-5, anti-IL-13	[112–114]
<b>Eosinophilic</b>	Avoidance of triggers, ICS, CS, anti-IgE, anti-IL-5, anti-IL-13	[115]
<b>Non-eosinophilic</b>	Macrolides, less likely to respond well to ICS	[116, 117]
<b>ABPA and SAFS</b>	Antifungals	[118, 119]
<b>Churg–Strauss syndrome</b>	Steroids, cyclophosphamide, rituximab	[120, 121]
<b>Exercise-induced asthma</b>	ICS	[122]
<b>Aspirin sensitive</b>	Avoidance of aspirin, leukotriene inhibition	[123]
<b>Occupational</b>	Avoidance of occupational agent	[124]

Aspirin sensitive and occupational subgroups appear to stay the same over time; other subgroups may vary according to treatment or the clinical picture is unclear. In each subgroup, some of the treatment options and relevant references are shown (see text for further details). All have shown either symptomatic improvement, reduction in exacerbations or both. Bronchodilator agents are not listed and should be used in all subgroups when required or other therapies with equal efficacy should be used. ABPA: allergic bronchopulmonary aspergillosis; SAFS: severe asthma with fungal sensitisation; ICS: inhaled corticosteroids; CS: corticosteroid; IL: interleukin.

T-helper (Th)2-high gene signature in airway epithelial tissue in 50% of mild asthmatics, and was associated with more atopy and response to ICS therapy [132]. The remaining patients showed a Th2-low gene signature similar to healthy controls, with less airway obstruction, lower hyperreactivity and lower response to ICS. This implies that selection could be applied to the use of ICS and, in particular, high-dose ICS, based on airway eosinophilia. Trials using this strategy have had some success [115], and it is supported by the latest severe asthma guidelines [114]. Newer drugs targeting severe eosinophilic asthma are also emerging; most are monoclonal antibodies that are likely to be used in highly selected populations. Examples include mepolizumab (anti-interleukin (IL)-5) [115], and lebrikizumab (anti-IL-13), the latter being useful in patients with elevated periostin [113]. However, the relationship between eosinophilia and other features of asthma, such as airway hyperresponsiveness, is by no means clear cut; indeed, they may be inherited separately [133], hence this cannot be the only way in which we define our phenotypes and design new treatments. Noneosinophilic disease has shown some response to macrolide therapy [116, 117], although this is not a widely recommended treatment strategy [114].

Other clinical features can be used to identify patients who fall into subgroups that may influence management. For instance, early-onset allergic, exercise-induced asthma (EIA) and ASA phenotypes belong to the Th2-high form of disease while neutrophilic asthma and smooth-muscle mediated paucigranulocytic asthma belong to the non-Th2 group [110]. Sputum cell counts may be impractical for routine phenotyping, particularly in primary care; hence, a detailed history (age of onset, atopy, aspirin sensitivity, smoking, *etc.*) is key to identifying subgroups and tailoring treatment in clinical practice. In allergic asthma, avoidance of triggers may be a strategy, although the utility of avoidance for house dust mite allergy is debatable [134]. Omalizumab is a well-validated strategy for allergic asthma with high IgE, which reduces corticosteroid use and exacerbation rates [135] and improves long-term control [136]. Patients with ASA should avoid aspirin and nonsteroidal anti-inflammatory drugs. Although there is some evidence that leukotriene inhibition is particularly effective in ASA, it is not consistent [123, 137] and standard asthma management should be followed.

History also identifies occupational asthma, which is best diagnosed by the occupational asthma system score on serial peak expiratory flow rate testing or specific provocation challenge [138]. It is subdivided into asthma precipitated by the exposure or pre-existing asthma that is worsened by exposure. Sputum eosinophil counts and *F*<sub>ENO</sub> relate reasonably well to specific provocation challenge [139], although distinct groups without *F*<sub>ENO</sub> elevation are identifiable [140]. Cessation or reduction of exposure is key, as delineated in a systematic review by a European Respiratory Society Task Force [124]. Patients with continued exposure tend to progress faster in terms of lung function decline and symptoms [141].

Fungal sensitisation in asthma is common with an estimated prevalence of up to 30% [142], covering a spectrum from allergic bronchopulmonary aspergillosis (ABPA) through severe asthma with fungal sensitisation (SAFS) and asymptomatic sensitisation. Diagnosis is made by examining serum IgE, and by performing specific radioallergosorbent tests to *Aspergillus* and *Aspergillus* precipitins. Both ABPA and SAFS respond to antifungals [118, 119], although their efficacy is debatable [114]. Susceptibility to fungal infection and sensitisation may be genetically determined (*e.g.* human leukocyte antigen type [143] and Toll-like receptors [144]).



Churg–Strauss syndrome is a rare, progressive, systemic disorder characterised by eosinophilia, extravascular necrotising granulomas, worsening asthma, lung infiltrates and eventually antineutrophil cytoplasmic antibody-positive systemic vasculitis [145]. Significant heterogeneity is seen at presentation and longer term. Lower baseline eosinophil counts predict mortality [146]. Precise management differs according to disease severity (e.g. presence of glomerulonephritis), but in general involves aggressive immunosuppression, often with cyclophosphamide alongside corticosteroids [120]. Rituximab has also been used with some success [121].

EIA is an acute transient airway narrowing that occurs during and, most often, after exercise. EIA is defined as a decrease in FEV<sub>1</sub> >10% from baseline measured up 30 min after exercise. A higher prevalence of EIA has been reported among elite athletes, especially in endurance sports, such as rowing and cross-country skiing, compared to the general population [147]. However, some elite athletes with EIA have neither a history of childhood asthma nor a family history of asthma, suggesting that environmental factors are more important than genetic inheritance [148]. The most effective therapy for EIA is regular use of ICS [122]. Early use of leukotriene inhibition may be equally effective [149, 150].

### *Subgroups with less clear implications for therapy*

Severe refractory asthma is an area of intense research, which many newer therapies are being targeted towards. However, this is also heterogeneous with eosinophilic and noneosinophilic phenotypes [151], implying that severity may not be the feature that drives specific treatment. Nevertheless, at least part of severe asthma has a different pathobiology compared to nonsevere disease. For example, innate immunity in the airway is influenced by glucocorticoids [152] and there have been recent insights into the role that innate immunity plays in steroid refractory severe disease [153].

Neutrophilic asthma also exhibits some innate immune features [154], although whether this is a true phenotype remains debatable. Neutrophilic asthma is associated with low FEV<sub>1</sub>, air trapping [155] and smoking [156], and thus may represent overlap with COPD, or indeed with other pro-inflammatory trigger factors. For instance, two studies have reported clusters of older, obese, female, nonatopic asthmatics [128, 157]. “Extensive remodelling asthma” is characterised by pronounced airway remodelling and minimal inflammation [158], increased airway smooth muscle mass may also occur. One cause may be an intrinsic airway smooth muscle abnormality. Whether extensive remodelling has therapeutic implications remains uncertain.

### *Reconciling variability and triggers with subgroup identification*

Unlike COPD, asthma is classically thought to be variable. This brings problems when defining subgroups, as patients may change over time or in response to treatment. We suggest that identifying the current subgroup is the most important factor when modulating therapy. Knowing the subgroup at initial diagnosis may also help but past features should not preclude altering treatment based on current presentation.

### *Triggers*

Specific trigger or detrimental factors are interesting elements of phenotyping. Classical triggers (allergens and occupation) that change treatment are part of our subgroup definitions. Recognised triggers that do not alter specific asthma management include obesity, smoking, gastro-oesophageal reflux disease (GORD), menstrual cycle and air pollution. Obesity is a risk factor for asthma, and asthma often causes weight gain; there is no consensus about the exact relationship between the two. One cluster analysis identified a noneosinophilic obese group of patients [128], another has reported a nonatopic obese group who required multiple courses of corticosteroids [157]. However, a recent meta-analysis reported that body mass index (BMI) was a key feature of asthma subgroups but, of the clusters that were predominantly obese, clinical and inflammatory differences occurred between them suggesting heterogeneity independent of obesity [159]. Weight loss appears to help asthma control [160]; however, since weight loss has pluripotent health benefits, we felt it did not represent specific asthma management. Smoking also influences the course of asthma. Asthmatics who smoke show poor response to corticosteroid therapy, more frequent exacerbations and worse lung function progressing to fixed obstruction, but smoking might make airways disease worse.

An association between asthma and GORD has been the subject of considerable investigation. There is no doubt that GORD is more common in asthma [161] and this has led to the suggestion that reflux treatment may improve asthma control. Several large clinical trials [162, 163] and a Cochrane review [164] have been published, demonstrating that treatment with high-dose proton-pump inhibitor improves cough but has no effect on asthma symptoms, lung function or exacerbation rates.

17% of asthmatic females report worsening of symptoms near menses, and this perimenstrual asthma phenotype is associated with higher BMI, lower forced vital capacity, GORD, aspirin sensitivity and poor asthma control [165]. However, healthy females exhibit similar changes in pulmonary physiology across their menstrual cycle to those with asthma [166], and multivariate analysis has shown that baseline asthma characteristics can differ in those who report symptom changes across their cycle [167]. As such, it is likely that sex hormones represent a trigger, and that perimenstrual asthma is not a truly different subtype.

#### *Constancy of asthma subgroups*

The constancy of asthma phenotypes over time, or after therapy implementation, is not as clear in COPD. Asthma is variable, thus phenotypes ought to change over time, but few published data exist. Those that appear to remain constant are occupational asthma and ASA. Occupational asthma progresses faster if exposure continues [124], implying that the underlying disease process is unchanged. The risk of precipitating severe exacerbations means that testing whether patients remain aspirin sensitive long-term has rarely been performed. Case reports demonstrate that aspirin sensitivity can develop in patients who have previously taken it without respiratory problems [168], but studies which have challenged known ASA patients have shown that most remain sensitive [169, 170]. Asthma subgroups that clearly change with treatment include ABPA, SAFS and Churg–Strauss syndrome. Atopy and allergy may also remit, usually over time but occasionally with treatment, such as desensitisation [171]. For example, 21% of children aged <2 years with severe peanut allergy will be tolerant by 5 years of age [172]. Remission of asthma was equally common in allergic/atopic and nonatopic patients in a large prospective cohort study of childhood-onset asthma, averaging 65% of patients [173]. Even in adults, allergic responses vary over time, as demonstrated by the fact that 39% of patients have different results on serial skin-prick testing (mostly gaining new allergies), but in 13% of cases allergies were lost and in 4% allergies were gained and lost [174].

Published evidence is inconsistent regarding the constancy of asthmatic airway inflammation. In adults, 50% of mild-to-moderate asthmatics have persistently noneosinophilic (often neutrophilic) disease and the remainder have persistent or intermittent eosinophilia [175]. Intermittent and persistent groups exhibited similar clinical characteristics, and hence may represent a milder form of the same population. Therapeutically, the neutrophilic patients respond poorly to usual asthma therapy. Conversely, the sputum inflammatory phenotype proved inconsistent in asthmatic children [176]. This may also change with treatment; for example, corticosteroids inhibit neutrophil apoptosis [177] such that neutrophilic asthma could actually represent over-treated eosinophilic asthma. This hypothesis is supported by the observation that corticosteroid withdrawal abolished neutrophilic subjects among moderate asthmatics [156].

#### **Subgroups shared between COPD and asthma**

When a patient presents with symptoms of increased variability of airflow alongside partially reversible airflow obstruction, it is known as the asthma–COPD overlap syndrome (ACOS) [178]. A consensus conference has proposed that an ACOS patient must fulfil two major criteria or one major and two minor criteria from the following. 1) Major criteria: positive bronchodilator response (>400 mL and >15% FEV<sub>1</sub>), sputum eosinophilia or previous diagnosis of asthma. 2) Minor criteria: increased total serum IgE, history of atopy or positive bronchodilator test (>200 mL and >12% FEV<sub>1</sub>) on at least two occasions [179]. ACOS typically includes patients with early-onset asthma and a long disease duration who then fulfil criteria for COPD with age, COPD patients with increased reversibility and smoking asthmatics who have fixed airflow obstruction. Overall, 13–19% of patients with obstructive lung diseases have some overlap and this increases with age [180, 181]. In the UPLIFT (Understanding Potential Long-term Impacts of Tiotropium) trial, two-thirds of moderate-to-severe COPD patients exhibited bronchodilator responsiveness [182]; however, most clinical trials for either asthma or COPD exclude patients with features of the other disease, implying that their results will be poorly generalisable in real-life. ACOS has been extensively reviewed elsewhere [178, 179]. Our reasoning for including it here is to revisit the concept in light of the more complex subgroups of both asthma and COPD that we have described. Its importance is that patients exhibiting features consistent with ACOS are more likely to be frequent exacerbators [183], have more respiratory symptoms, higher mortality [183], higher comorbidity rates [184], greater healthcare utilisation [184] and worse HRQoL [181].

Overlap patients are generally thought to exhibit phenotypes part way between COPD and asthma. For example, GIBSON and SIMPSON [178] reported prevalence of atopy that was highest in asthma (100%) intermediate in ACOS (64%) and lowest in COPD (25%). There are some differences that may depend on the predominant pathology. Positive bronchodilator response observed in COPD is associated with increased eosinophilic inflammation [185] whilst irreversible COPD more frequently exhibits neutrophilia. Smoking asthmatics typically have inflammatory features that resemble COPD with increased neutrophilia and sometimes airway remodelling [186]. Classical asthma drivers, such as occupation, are associated with fixed airflow obstruction after chronic exposure [187] and ABPA has also been reported in patients with COPD [188].

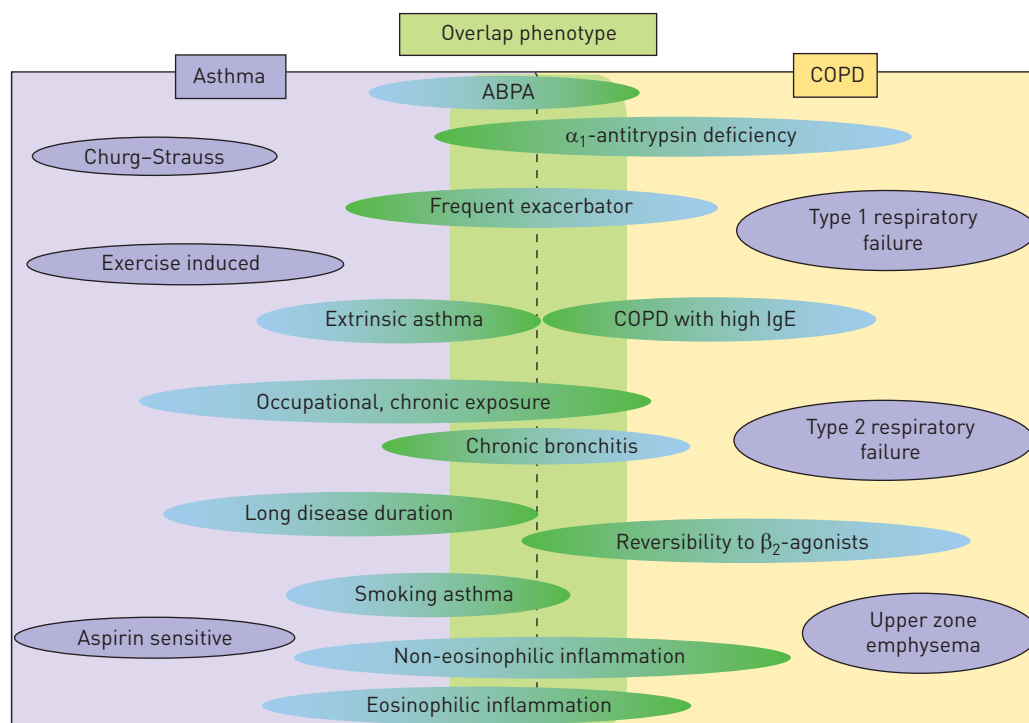


FIGURE 2 Schematic diagram of the shared subgroups between asthma and chronic obstructive pulmonary disease (COPD). The figure shows phenotypes that are recognised in both conditions. The placement/colour of the shapes indicates the degree to which they are recognised in asthma and COPD. ABPA: allergic bronchopulmonary aspergillosis.

During exacerbations of ACOS, airway mucosal eosinophils increase more than neutrophils [189] explaining the improvement with systemic corticosteroids or ICS. Conversely, analysis of volatile organic compounds in severe persistent asthma compared to severe COPD showed that volatile organic compound patterns remained different, suggesting singular pathophysiological mechanisms [190]. Taken together, the evidence suggests that there may be aspects of shared pathogenesis that move treatment decisions to that of the subgroup irrespective of the primary diagnosis. Shared subgroups are shown in figure 2.

#### Examples of subgroups common to asthma and COPD

The evidence for treating overlap is far less extensive than for single pathology. In addition, it would be beyond the scope of this article to review all shared subgroups comprehensively; thus, we have chosen a few pertinent examples. One significant shared phenotype where evidence exists for management is eosinophilic airways disease. The evidence that asthmatics with eosinophilia respond to steroids is incontrovertible, and a study from Leicester, UK, has demonstrated that patients with COPD and relatively high blood eosinophils (>2%) respond better to oral steroids in the context of an exacerbation than those with lower levels [70]. Similar results have been reported for use of ICS [25–27, 69].

Frequent exacerbations in asthma can be associated with risk factors such as severe nasal sinus disease, GORD, recurrent respiratory infections and obstructive sleep apnoea [191]. Many, such as GORD, are similar to the risk factors for frequent exacerbation in COPD patients in the ECLIPSE study [51]. Similar strategies to manage risk factors are advocated in both diseases, alongside potential additional therapies such as macrolides [10, 116, 192].

#### Messages for clinical practice

Characterising patients with chronic respiratory symptoms may be more important than giving a label of asthma or COPD in predicting prognosis and response to treatment. A lot of phenotypes have been defined in the literature but some of them do not yet have treatment or prognostic implications. Asthma subgroups, unlike COPD, are likely to change over time and the current phenotype should be regarded as the most important factor to guide treatment.

#### Acknowledgements

We would like to thank GSK for organising the European Respiratory Network of Excellence event that stimulated the debates leading to this review.

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